Table 13: Continued

Proposal	*Contradiction*
Continued:	
also contains components structurally similar to compounds [(+)-catechin, esculetin, esculin (Liu and Castonguay, 1991; Teel and Castonguay, 1992)] that have been reported to act as antitumorigens and/or antimutagens to NNAs.	
§ A variety of tobacco components and other compounds structurally similar to tobacco or smoke components are known to inhibit the *N*-nitrosation of secondary and tertiary amines to NNAs, a reaction known to occur among the nitrogen oxides, amino compounds, and water during the tobacco smoking process. These inhibitors of NNA formation include several primary amines, ascorbic acid and ascorbates (Mirvish *et al.*, 1972; Mirvish and Shubik, 1974; Archer *et al.*, 1975; Mirvish, 1981a, 1981b, 1986), indole, the tocopherols (particularly α-tocopherol) (Mergens *et al.*, 1978; Mirvish, 1986), the carotenes, several phenols, and polyphenolic compounds such as chlorogenic acid (*cf.*, Brunnemann and Hoffmann, 1991a, 1991b). *NOTE:* The effect of these compounds on the *N*-nitrosation reaction should be differentiated from the effect of some of the same compounds on the tumori-genicity or mutagenicity of various NNAs, *e.g.*, inclusion of ascorbic acid or ascorbate in the reaction substantially reduces the yield of NNAs; administration of ascorbic acid with a tumorigenic NNA such as NNK substantially reduces the tumorigenicity in laboratory animals. Little study has been devoted to determining whether compounds such as those noted above would exert a beneficial effect on MS properties if added to cigarette tobacco because of diminished *N*-nitrosation with resulting lower NNA delivery or because of the simultaneous delivery of the antitumorigen or anti-mutagen together with the NNAs.	
§ Because of the nature of the cigarette smoke aerosol, Wynder and Hoffmann (1961a) considered selective filtration of a specific smoke component or class of smoke components such as the PAHs to be an "impossibility."	§ Selective filtration is not "impossible." Wynder and Hoffmann (1962b) reversed their view on the impossibility of selective filtration when they found that relatively volatile smoke components, *e.g.*, low molecular weight phenols, are selectively removed from the MS stream by filters incorporating certain plasticizers, *e.g.*, triacetin (*cf.*, Laurene *et al.*, 1963). Some years later, the same phenomenon was observed with VNAs (Fredrickson, 1965/1967; Brunnemann *et al.*, 1977).

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Table 13: Continued

Proposal	*Contradiction*
§ Guerin *et al.* (1992) estimated the exposure to NNAs in ETS-filled rooms to be low: NDMA, < 10-40 ng/m^3; NDEA, 3 ng/m^3; NPYR, 3 ng/m^3; NNN, < 1-3 ng/m^3; NNK, < 1-3 ng/m^3.	§ Consumers are exposed daily to NNAs from a variety of nontobacco sources. Many foodstuffs, beverages, and cosmetics contain appreciable levels of some of the volatile NNAs also identified in tobacco and/or tobacco smoke (Magee and Barnes, 1967; Sebranek and Cassens, 1973; Preussmann and Eisenbrand, 1984; Maga, 1988; Bailey and Williams, 1993). Daily nontobacco exposure (primarily dietary) to NNAs is estimated to exceed 1,800 ng/person; daily nontobacco source exposure to NDMA is estimated to exceed 1,100 ng/person (Preussmann and Eisenbrand, 1984). *NOTE:* These estimates are based on analytical data that may have included values for NNAs artifactually generated during the analytical procedure.

Exposure to N-Nitrosamines from Non-Tobacco Sources

Among several groups who have been involved in research on NNAs since soon after their tumorigenicity in laboratory animals was first reported by Magee and Barnes (1956) were Barnes, Magee, and Schoental in the U.K. and Dontenwill, Druckrey, Preussmann, and Schmähl in Germany. From the German group, Preussmann has been a key contributor to our knowledge of NNAs. He has authored/coauthored research results and review articles continuously on NNAs since 1959. Initially, Preussmann was involved with the investigation of the relationship between the structure of an NNA and its tumorigenicity (Druckrey *et al.*, 1961). In 1962, Druckrey and Preussmann (1962) proposed the possibility of the formation of NNAs in tobacco smoke from the secondary amines, nitrogen oxides, and water present. For the next two decades, Preussmann investigated methods of NNA analysis (Preussmann *et al.*, 1964; Egan *et al.*, 1983); tumorigenicity of various NNAs (Druckrey *et al.*, 1967, 1968; Habs *et al.*, 1981; Magee *et al.*, 1976; Janzowski *et al.*, 1978a, 1978b; Ketkar *et al.*, 1982, 1983; Zerban *et al.*, 1988); the involvement of nitrate and nitrite in NNA formation (Spiegelhalder *et al.*, 1974); NNAs in foods (Spiegelhalder *et al.*, 1980), beverages (Spiegelhalder *et al.*, 1979, 1983), toiletries Spiegelhalder and Preussmann, 1984).

In the late 1980s, Preussmann returned to the study of NNAs in tobacco and tobacco smoke and the question of the possible endogenous formation of TSNAs in smokers (Tricker *et al.*, 1988, 1989, 1991, 1992; Tricker and Preussmann, 1988a, 1988b, 1989, 1991; Fischer *et al.*, 1989a, 1989b, 1989c, 1990a, 1990b, 1990c, 1990d, 1991a, 1991b; Spiegelhalder *et al.*, 1989a, 1989b; Kumar *et al.*, 1991).

Discussing the escalation in publications on *N*-nitroso compounds, Preussmann (1983b) wrote:

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> ...At present (1981), more than 1400 papers are published annually on the analysis, formation, chemistry, biochemistry, metabolism and biological effects of *N*-nitroso compounds.
>
> ...[T]here is no equivocal and convincing evidence of carcinogenicity in humans of *N*-nitroso compounds. Therefore, an answer is needed to the question whether exposure to traces of these compounds from the general environment...poses a risk to human health. In this situation animal data must be extrapolated to man, with all the inherent uncertainties.

Preussmann and Stewart (1984) noted the exponential increase in publications on NNAs between 1972 and 1984 and estimated that about three papers were published daily on this topic in the scientific literature in 1983. They also cautioned:

> Patterns of investigations established with nitroso compounds are being extended to more structurally complex carcinogens. Yet the contribution of nitroso compounds to the burden of environmentally determined neoplasia in humans remains to be determined... The priority that might reasonably be placed on reducing human exposure to nitroso compounds could be better judged if the number of cancers likely to be affected by such measures were known.

In this memorandum, discussions are limited primarily to the NNAs common to tobacco/tobacco smoke and the other exposures (foodstuffs, beverages, cosmetics, drugs, etc.). As described by Preussmann and Stewart (1984), various bioassays on laboratory animals have been conducted on over 330 different NNAs (220) and *N*-nitrosamides (110). Fewer than 40 of these *N*-nitroso compounds have been identified in tobacco and/or tobacco smoke.

- *Foodstuffs and Beverages*

Historically, the search for tumorigenic compounds in foodstuffs and beverages began in the early 1930s, shortly after the demonstration that the synthetic PAH DBA and the coal tar isolate BaP were carcinogenic when painted on mouse skin and sarcogenic when injected subcutaneously. The initial investigations were limited to attempts to demonstrate the presence of these and similar polycyclic aromatic hydrocarbons in heated foodstuffs (meat, fish, etc.), particularly those containing cholesterol and its derivatives.

Subsequent to the demonstration of the tumorigenicity in laboratory animals of NNAs such as *N*-nitrosodimethylamine (NDMA) (Barnes and Magee, 1954; Magee and Barnes, 1956), the search for NNAs in commonly used foods and beverages began. Despite nearly half a century of study of food components tumorigenic to laboratory animals, caution was recommended as recently as 1984 in the interpretation of the laboratory findings. *E.g.*, Grasso (1984) in his review of carcinogens in food noted:

> Carcinogens occur at very low concentrations in food so that if any type of tumors result at all, the number is expected to be very low indeed. At present much thought is being given to the relative hazards of these levels and how they can be assessed. Certainly no firm association has been established between any human cancer and the low levels of carcinogens in food, but this problem may only reflect the imperfect state of current epidemiological investigations.

Despite hundreds of publications on the presence of NNAs in foods and beverages and the

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results of bioassays with NNAs in laboratory animals, Grasso also wrote:

> Despite intensive experimental investigations, however, the hazard to humans from small doses of nitrosamines present in our food and water are difficult to assess, and until further experimental evidence is available, no firm opinion can be given.

This opinion is almost identical with that of Preussmann and Stewart (1984) who reviewed not only the human exposure to NNAs in foods, beverages, water, drugs, cosmetics, etc. but also exposure to the NNAs (volatile, nonvolatile and tobacco-specific) in tobacco products:

> Although estimates of the total human burden caused by exposure to nitroso carcinogens have been attempted..., we do not think that sufficient data exist for meaningful evaluation; therefore, estimation of nitrosamine contribution to human cancer risk is largely speculative. Premature calculations are liable to be misinterpreted by those who are not thoroughly familiar with the multitude of uncertainties and difficulties inherent in such calculations, especially when estimates of lifetime risks are based on such figures.

Table 14 lists the levels (ng/g) of several NNAs identified in commonly used foods and beverages; **Table 15** summarizes the studies in which various NNAs were identified in foods and beverages. One of the earliest investigators of NNAs in foodstuffs was Kröller (1967) who identified NDMA in cheese. Kröller's studies were not limited to possible tumorigens in foodstuffs. From 1963 through 1966, he also investigated the pyrosynthesis of PAHs, particularly BaP, in cigarette smoke and from various materials used in cigarette fabrication, *e.g.*, cigarette paper, adhesives, humectants, dyes, inks, flavorants, tobaccos (see summary, Wynder and Hoffmann, 1967).

Also included in **Table 14** are data for the per cigarette deliveries of several NNAs identified in foods and beverages. From these data, comparisons of the relative exposures from foods, etc. and cigarette smoke are possible, *e.g.*, the per cigarette MS range for NDMA has been reported as 1.7-97 ng. Since one ounce is approximately 30 g, a person eating 1 oz of bacon would be exposed to 30 (1-9.5) or 30-285 ng of NDMA. Similarly for cured meat, the per cigarette exposure of 1.7-9.7 ng should be compared to the dietary exposure of 30-2,400 ng from eating 1 oz of cured meat or 300-3,150 ng from eating 1 oz of sausage!

Over the years, numerous reports (*cf.* Neurath *et al.*, 1964; Krull *et al.*, 1978; Eisenbrand *et al.*, 1983; Caldwell and Conner, 1989, 1990) on the artifactual formation of NNAs during the collection and analysis of tobacco smoke and the various remedial procedures taken to minimize this problem have been published. Similar problems were noted by Wolff and Wasserman (1972) on inflated levels of NNAs reported in foodstuffs and beverages. They expressed reservations about the validity of pre-1972 analytical methodology since later studies demonstrated that the earlier procedures introduced both artifact and error. Thus, the levels of NNAs reported in foodstuffs were actually lower than those reported prior to 1972. In 1986, Sen *et al.* (1986) proposed improvements in analytical methodology to prevent artifactual formation and subsequent inflated levels of NNAs in rubber products; propyl gallate was demonstrated to be an effective inhibitor of *N*-nitrosation during the analytical procedure.

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TABLE 14: *N*-NITROSAMINES IN FOODS AND BEVERAGES (ng/g)

Food or Beverage	NDMA[a]	NDEA	NPYR	NPIP
Meat				
Bacon, uncooked	1-9.5	0-2	≤17	0
Bacon, fried	0.1-28	1-4	3-44	1
Cured meats	1-80	≤40	10-105[d]	≤60[d]
Fish				
Fresh or frozen	3-18	1-2	—	—
Salted or pickled	1-35	50-108	0-37	—
Smoked, baked, or processed	6-177	≤147	—	—
Vegetables/vegetable oils				
Beans	0	0-0.2	—	—
Vegetables[b]	0	0	—	—
Soybean oil[c]	0-20	0-4	—	—
Cheeses	0.1-68	—	—	2-11
Beverages				
Water	0.8-3.3	0.1-1.83	0.09-0.2	0.03
Alcohol beverages	≤10	≤0.1	—	—
Cigarette Mainstream Smoke (ng/cigt)	1.7-97	0-4.8	2.6-52	

[a] NDMA = *N*-nitrosodimethylamine; NDEA = *N*-nitrosodiethylamine; NPYR = *N*-nitrosopyrrolidine; NPIP = *N*-nitrosopiperidine
[b] 16 different vegetable species tested
[c] Freshly refined
[d] Levels in sausage

A variety of investigations has been conducted during the past decade on exposures to NNAs, and a few will be cited here. Okieimen *et al.* (1985) reported on the *total* NNAs content of beer, dairy products, bouillon cubes, and tobacco products. They reported that dairy products showed the lowest total value; bouillon cubes, the highest. Mandagere (1986) reported on the high NNAs levels in a variety of meats cured via a smoking process.

Coker *et al.* (1991b) tested some 200 commercial foodstuffs for NNAs and noted the values for beverages were high, those for dairy products low. Craddock (1990) and Sen (1991) found NNA levels in Canadian foodstuffs and beverages to be similar to those for U.S.A. products. Since the review by Preussmann and Stewart (1984) on the tumorigenicity of NNAs and that by Preussmann and Eisenbrand (1984) on exposure to NNA tumorigens in the environment, numerous detailed reviews of NNA exposures (alcoholic beverages, meats, seafood, cosmetics, tobacco, rubber goods, metal cutting oils, pharmaceuticals, environment,

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TABLE 15: VOLATILE AND NONVOLATILE *N*-NITROSAMINES IN FOODSTUFFS AND BEVERAGES

N-Nitrosamine: Foodstuff/Beverage	Reference
N-nitrososarcosine (NSAR) {acetic acid, 2-methylnitrosamino)-}	
meat	Hamburg and Kann, 1982
beer (and malt)	Pollock, 1981; Sen *et al.*, 1983
N-nitrosodibutylamine (NDBA) {1-butanamine, *N*-butyl-*N*-nitroso-}	
fish	Huang *et al.*, 1981
N-nitrosodiethylamine (NDEA) {ethanamine, *N*-ethyl-*N*-nitroso-}	
bacon	Crosby *et al.*, 1972; Wasserman *et al.*, 1972
fish	Sen *et al.*, 1970; Crosby *et al.*, 1972; Wasserman *et al.*, 1972; Fong and Chan, 1973, 1976; Huang *et al.*, 1981
cheese	Crosby *et al.*, 1972; Wasserman *et al.*, 1972
powdered milk	Maduagwu and Bassir, 1979
beer (and malt)	Spiegelhalder *et al.*, 1979; Scanlan *et al.*, 1980; Kawabata *et al.*, 1982
N-nitrosodimethylamine (NDMA) {methanamine, *N*-methyl-*N*-nitroso-}	
meat, cured meat	Wasserman *et al.*, 1972; Panalaks *et al.*, 1973, 1974; Sen, 1972; Spiegelhalder *et al.*, 1980; Eisenbrand, 1981; Helgason *et al.*, 1984
bacon	Crosby *et al.*, 1972; Wasserman *et al.*, 1972; Vecchio *et al.*, 1986
fish	Sen *et al.*, 1970; Crosby *et al.*, 1972; Wasserman *et al.*, 1972; Fong and Chan, 1973, 1976; Iyengar *et al.*, 1976; Havery and Fazio, 1977; Kawabata *et al.*, 1979; Maki *et al.*, 1979; Josefsson and Nygren, 1980; Masami *et al.*, 1980; Huang *et al.*, 1981; Pedersen and Meyland, 1981; Röper *et al.*, 1981; Nieper and Etzel, 1983; Röper, 1983
squid	Kawabata *et al.*, 1979; Maki *et al.*, 1979; Masami *et al.*, 1980
cheese	Kröller, 1967; Crosby *et al.*, 1972; Wasserman *et al.*, 1972; Goodhead *et al.*, 1976; Havery *et al.*, 1976; Gough *et al.*, 1977; Eisenbrand *et al.*, 1978; Elgersma *et al.*, 1978; Danish Institute of Protein Chemistry, 1980; Spiegelhalder *et al.*, 1980; Eisenbrand, 1981

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Table 15: Continued

N-Nitrosamine: Foodstuff/Beverage	Reference
N-nitrosodimethylamine (NDMA) {methanamine, *N*-methyl-*N*-nitroso-} (*cont.*)	
powdered milk	Maduagwu and Bassir, 1979; Libbey *et al.*, 1980; Lakritz and Pensabene, 1981; Havery *et al.*, 1982
wheat flour	Hedler and Marquardt, 1968
beer (and malt)	Sen and Dalpe, 1972; Goff and Fine, 1979; Spiegelhalder *et al*, 1979, 1980; Walker *et al.*, 1979; USFDA, 1980; Maki *et al.*, 1980a, 1980b; Preussmann *et al.*, 1980, 1982b; Scanlan *et al.*, 1980; Sen *et al.*, 1980a; Stephany and Schuller (1980); Eisenbrand, 1981; Havery *et al.*, 1981; Hotchkiss *et al.*, 1981; Sen and Seaman, 1981a, 1984; Slack and Wainwright, 1981; Kann *et al.*, 1982; Kawabata *et al.*, 1982; Mangino *et al.*, 1982; Spiegelhalder, 1983a; Jasinski, 1984; Scanlan *et al.*, 1980; Scanlan and Barbour, 1991
Scotch whiskey	Goff and Fine, 1979
brandy (French)	Walker *et al.*, 1979
other alcohol beverages	Sen and Dalpe, 1972; Gough, 1977; Bassir and Maduagwu, 1978
N-nitrosomorpholine (NMOR) {morpholine, 4-nitroso-]	
fish	Fong and Chan, 1973, 1976
N-nitrosopiperidine (NPIP) {piperidine, 1-nitroso-}	
meat, cured meat	Spiegelhalder *et al.*, 1980; Eisenbrand, 1981
bacon	Crosby *et al.*, 1972; Wasserman *et al.*, 1972; Vecchio *et al.*, 1986
fish	Crosby *et al.*, 1972; Wasserman *et al.*, 1972
squid	Kawabata *et al.*, 1979; Masami *et al.*, 1980
cheese	Crosby *et al.*, 1972; Wasserman *et al.*, 1972
N-nitrosodipropylamine (NDPA) {1-propanamine, *N*-nitroso-*N*-propyl-}	
fish	Sen *et al.*, 1970; Huang *et al.*, 1981

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Table 15: Continued

N-Nitrosamine: Foodstuff/Beverage	Reference
N-nitrosopyrrolidine (NPYR) {pyrrolidine, *N*-nitroso-}	
meat, cured meat	Pensabene *et al.*, 1979; Spiegelhalder *et al.*, 1980; Eisenbrand, 1981; Theiler *et al.*, 1984; Alldrick *et al.*, 1985
bacon	Hansen *et al.*, 1977; Sen *et al.*, 1977, 1979; Gough *et al.*, 1978; Havery *et al.*, 1978; Janzowski *et al.*, 1978b; Cross and Bharucha, 1979; Gray and Randall, 1979; American Meat Institute, 1980; Nitrite Safety Council, 1980; Webb and Gough, 1980; Josefsson and Nygren, 1981; Fazio *et al.*, 1982; Gray, 1982; Pensabene *et al.*, 1982; Alldrick *et al.*, 1985; Vecchio *et al.*, 1986
fish	Crosby *et al.*, 1972; Wasserman *et al.*, 1972; Kawabata *et al.*, 1979; Masami *et al.*, 1980
cheese	Crosby *et al.*, 1972; Wasserman *et al.*, 1972
beer (and malt)	Spiegelhalder *et al.*, 1979; Scanlan *et al.*, 1980; Kawabata *et al.*, 1982; Jasinski, 1984
N-nitrosoproline (NPRO) {2-pyrrolidinecarboxylic acid, 1-nitroso-}	
meat	Pensabene *et al.*, 1979; Hamburg and Hamburg, 1982; Dennis *et al.*, 1984; Dunn and Stich, 1984; Helgason *et al.*, 1984; Sen and Seaman, 1984
bacon	Hansen *et al.*, 1977; Brunnemann *et al.*, 1984b; Sen and Seaman, 1984; Massey *et al.*, 1991
chicken	Brunnemann *et al.*, 1984b
ham	Brunnemann *et al.*, 1984b
toast	Brunnemann *et al.*, 1984b
biscuits	Brunnemann *et al.*, 1984b
cornflakes	Brunnemann *et al.*, 1984b
beer (and malt)	Pollock, 1981; Sen *et al.*, 1983; Brunnemann *et al.*, 1984b
N-nitrosodiethanolamine (NDELA) {diethanolamine, *N*-nitroso-}	
meat, cured	Coker *et al.*, 1991a

water) have been presented by Mejstrik *et al.* (1987), Tricker and Preussmann (1988a), Tricker *et al.* (1989), Ellen (1990), and Matsui and Kaya (1992).

The daily intake of NNAs from ETS may be estimated if the following assumptions are made:

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- The average hourly intake of air is independent of whether the host is awake or asleep and is 1 m^3.
- The NNA level due to ETS is at the high end of the range estimated by Guerin *et al.* (1992) for the various NNAs, *i.e.*, 40 ng/m^3 for NDMA, 3 ng/m^3 for NDEA, NPYR, NNN, and NNK.
- None of the daily intake of the NNAs, whether from diet, ETS, and the like, is eliminated by exhalation, etc.
- The measured values reported for NNAs in diet, ETS, etc.

From the dietary NNA data of Preussmann and Eisenbrand (1984), Preussmann *et al.* (1980), and Spiegelhalder *et al.* (1980) and ETS NNA data summarized by Guerin *et al.* (1992), the following comparison was developed:

	Dietary Intake, ng/day				
Country	NDMA	NDEA	NPYR	NPIP	Total
Federal Republic of Germany	1,100[a]		100-150	10	1,210-1,260
United Kingdom					530
Japan					1,780
The Netherlands					1,100

	Intake from ETS[b], ng/day					
	NDMA	NDEA	NPYR	NPIP	NNN + NNK	Total
Estimated from German, Japanese, and American ETS Studies[c]	960	72	72		144	1,248

[a] Because of the reduction in NDMA in beer after 1979, this number is now probably closer to 700 ng/day
[b] On basis of the assumptions listed previously
[c] Brunnemann *et al.* (1978), Stehlik *et al.* (1982), Matsushita and Mori (1984), Klus *et al.* (1987); unfortunately, the TSNA results from a more recent study on ETS by Brunnemann *et al.* (1992) were not included in the assessment by Guerin *et al.* (1992) or Holcomb (1993)

It is obvious that the estimated exposure to the NNAs in diet *vs* ETS differs from the BaP exposure case. Whereas the dietary exposure to BaP was between 20 and 90 times the exposure to BaP in ETS, the dietary exposure to NNAs is essentially the same as the exposure to NNAs in the average diet.

Previously, the review by Holcomb (1993), his proportioning of male and female respiration rates during the day, his use of 11% particle retention, and his comments on the contribution of ETS to PAH exposure were discussed (see *Polycyclic Aromatic Hydrocarbons*). His summary of the NNA situation was as follows:

> Two studies [Stehlik *et al.*, 1982; Hoffmann *et al.*, 1987] have reported the presence of...(NDEA) and...(NDMA) in smoke-filled rooms... These are not tobacco-specific nitrosamines. The lack of

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reported background levels and the unusually high level of smoking prevents the evaluation of ETS contribution of these substances. Other nitrosamines reported to be found in tobacco smoke have either not been monitored or not been reported in ambient air where ETS is present.

Unlike the volatile NNAs which are found primarily in the vapor phase, the TSNAs are predominantly particulate-phase components[e]. Thus, their intake and retention should be proportional to the intake and retention of ETS particles. If Holcomb's assigned values for respiration rates during the day and his use of 11% retention are applied to the TSNA values in the above summary, the intake of NNN plus NNK will be much less than the 144 ng/day indicated. It probably would be less than 10 ng/day. As noted previously [*Polycyclic Aromatic Hydrocarbons (PAHs)*], if the more recent data of McAughey *et al.* (1994) for the % retention of particulates from *aged and diluted SS* be used in the calculations (17 to 41%, depending on analytical procedure and subjects' gender), the estimated exposure to NNN plus NNK will not be as low as if the 11% retention from the Hiller *et al.* (1982a, 1982b) study be used.

Brunnemann *et al.* (1992) determined the levels of several TSNAs in bars (3), restaurants (2), a car, trains (2), an office, and a smoker's private residence. The values reported and the subsequent description of the values found are shown below:

	TSNAs in Indoor Air, ng/m³			
Reference	NNN	NAT	NNK	Total of 3 TSNAs
Brunnemann *et al.* (1992)	ND[a] [b] - 22.8	ND[b] - 9.5	1.4 - 29.3	1.4 - 61.6
Hoffmann *et al.* (1994)	1.8 - 23	1.5 - 10	1 - 29	4.3 - 62

[a] ND = not detected

[b] Not detected in 5 of the 10 sites monitored (a restaurant, both trains, the office, smoker's residence)

In their discussion of exposure to TSNAs in ETS at various sites, Hoffmann *et al.* (1994) — perhaps to embellish the situation — apparently disregarded the fact that no NNN nor NAT was detected in half the test sites! Hoffmann *et al.* (1994) list total TSNAs in the MS from two different U.S. cigarettes at 979 and 670 ng/cigt. Thus, at an exposure level of 62 ng/m³ and a respiration rate of 1 m³/hr, it would require a nonsmoker to remain for nearly 16 and 11 hours in such an atmosphere to be exposed to similar levels of TSNAs as a smoker who inhales the mainstream smoke from the two cigarettes, respectively. Such a period surely exceeds the "several hours" noted by Hoffmann *et al.* (1994).

- *Pharmaceuticals*

Analysis of 68 commercially available drug preparations containing aminopyrine indicated that all contained NDMA (Schoenhard *et al.*, 1978). The following ranges for the NDMA levels were reported: 35 samples, 1-10 ppb; 27 samples, 11-50 ppb; 5 samples, 51-100 ppb; 1 sample,

[e] Although data are sparse, there is some evidence to indicate that TSNAs in ETS may be distributed between the vapor and the particulate phases.

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370 ppb. More recently, Preussmann and Eisenbrand (1984), Mejstrik *et al.* (1987), Lijinsky (1990), Ellen (1990), and Matsui and Kaya (1992) have reviewed the studies on the detection of NNAs in pharmaceuticals as well as in other consumer products.

- *Cosmetics*

Examination of a series of cosmetics widely used in the U.S.A. revealed that 27 of 29 sample contained NDELA. Levels varied from 1 to 48,000 ppb (Fan *et al.*, 1977). From a similar study conducted several years later, Klein *et al.* (1981) reported that five of ten cosmetic samples contained NDELA at levels ranging from 20 to 4,113 ppb. Despite the concern about the possible tumorigenicity of NDELA, its use in cosmetics has continued since its ban as an agricultural chemical in the U.S.A. in 1981 (EPA, 1981). Although none of the three has been identified in tobacco or tobacco smoke to date, *N*-nitrosomethyldodecylamine (in 6 of 7 products tested), *N*-nitrosomethyloctadecylamine, and *N*-nitrosobenzylmethylamine were identified in various commonly used cosmetics (Hecht, 1981). Fan *et al.* (1977) described an analytical method to determine NDELA in various cosmetics and shampoos; this procedure was updated by Fine (1983). Erickson *et al.* (1985) reported the presence of NDELA and similar compounds in cosmetics. Preussmann and Eisenbrand (1984) commented on the rapid absorption of NDELA in rats when administered by a variety of routes (subcutaneous, oral, intratracheal).

Preussmann and Eisenbrand (1984), Mejstrik *et al.* (1987), Ellen (1990), Lijinsky (1990), and Matsui and Kaya (1992) have reviewed the findings on the detection of NNAs in cosmetics. Spiegelhalder and Preussmann (1984) described the volatile and nonvolatile NNAs found in many samples of toiletries and cosmetics. Eisenbrand *et al.* (1991) reported a series of *N*-nitrosodialkylamines in cosmetics.

- *Rubber Products*

Investigations (Spiegelhalder and Eisenbrand, 1982; Spiegelhalder, 1983b) of various rubber products that come in frequent contact with human tissue revealed the presence of several NNAs. Baby-bottle nipples and pacifiers contained appreciable levels of NDMA, NDEA, *N*-nitrosodibutylamine (NDBA) (Thompson *et al.*, 1984), and NPIP. NDMA and NDBA were found in various rubber toys; these two NNAs plus NPIP were also found in rubber gloves. In their study of NNAs in rubber products, Sen *et al.* (1984), in their analysis of 30 samples, reported the detection of NMOR in various rubber products in addition to NDMA, NDEA, NDBA, and NPIP. Solenova *et al.* (1990) reported the presence of NDMA and NDEA.

- *Pesticides*

Several NNAs have been identified in pesticides used on various vegetable crops, *e.g.*, NDMA (Ross *et al.*, 1977) and NDPA (Zweig *et al.*, 1982).

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- *Water Supplies*

Most water supplies show little evidence of volatile or nonvolatile NNAs. However, water deionized by passage through various anion-exchange resins containing trialkylammonium compounds were reported to show NDMA levels ranging from 0.03 to 0.34 μg/liter (Fiddler *et al.*, 1972; Fine *et al.*, 1977a, 1977b; Gough *et al.*, 1977; Cohen and Bachman, 1978; Kimoto *et al.*, 1980).

- *Occupational and Industrial Exposures*

On the subject of industrial and occupational exposures to NNAs, Preussmann and Eisenbrand (1984) wrote:

> Data on occupational exposure to different nitrosamines are recent and not yet representative or complete. Nevertheless, the data indicate that certain industries have a serious nitrosamine problem and that the highest known concentrations of preformed *N*-nitrosamines occur in the workplace, especially in the rubber and leather industries... Exposures have been shown to vary considerably in regard to amount and type of nitrosamine found in different working places in several industries and occupations.

Preussmann and Eisenbrand (1984) summarized the following situations: In the rubber industry, workers were exposed to NDMA, NDEA, NMOR, and NPIP. In their study of the atmospheres in 132 sites in 12 rubber-processing plants in France, Ducos and Gaudin (1986) reported the detection of NDMA, NDEA, and NMOR in 93%, 27%, and 13% of the sites surveyed, respectively.

In the leather-tanning industry, exposures to NDMA (Bailey *et al.*, 1982; Skrabs, 1984; Wolf *et al.*, 1984), NDEA (Skrabs, 1984; Wolf, 1989), and NMOR (Wolf, 1989) occur.

Exposures to NDELA (Erickson *et al.*, 1985) in the cutting oils used in machine shops and to NDMA and NDEA (Wolf *et al.*, 1984; Wolf, 1989) in foundries have been reported .

In a plant producing rocket fuels, including 1,1-dimethylhydrazine by reduction of NDMA, workers were exposed to extremely high levels of NDMA. Shortly after this high exposure was recorded, the factory ceased manufacture of the 1,1-dimethylhydrazine.

In chemical and pharmaceutical factories where amines are used in production, exposures to NDMA and NDEA have been reported.

- *Comparison Summary of Exposures to* N-*Nitrosamines*

In **Table 16** is presented a simplified summary of the possible exposures to non-tobacco-specific NNAs that are known components of tobacco smoke. All ten NNAs listed in **Table 16** are found not only in tobacco smoke but also in a great variety of commonly consumed food-stuffs and beverages.

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TABLE 16: NON-TOBACCO EXPOSURES TO TOBACCO/TOBACCO SMOKE-RELATED *N*-NITROSAMINES

	N-Nitrosamine[a]									
	NDMA	NDEA	NDPA	NDBA	NDELA	NPIP	NPYR	NPRO	NMOR	NSAR
Consumer Good or Environment										
tobacco, tobacco smoke[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
food, beverages	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
rubber goods	✓	✓		✓		✓			✓	
cosmetics					✓					
pharmaceuticals[c]	✓									
pesticides[c]	✓		✓							
water	✓									
industrial environments										
rubber-processing plants	✓	✓				✓				✓
leather tanneries	✓	✓								✓
foundries	✓	✓								
machine shops					✓					

[a] NDMA = *N*-nitrosodimethylamine; NDEA = *N*-nitrosodiethylamine; NDPA = *N*-nitrosodipropylamine; NDBA = *N*-nitrosodibutylamine; NDELA = *N*-nitrosodiethanolamine; NPIP = *N*-nitrosopiperidine; NPYR = *N*-nitrosopyrrolidine; NPRO = *N*-nitrosoproline; NMOR = *N*-nitrosomorpholine; NSAR = *N*-nitrososarcosine

[b] In addition to the *N*-nitrosamines listed, tobacco and tobacco smoke contain a variety of tobacco-specific *N*-nitrosamines and *N*-nitrosamino acids other than *N*-nitrososarcosine.

[c] *N*-Nitrosamines other than those determined in tobacco and/or tobacco smoke have also been detected in various pharmaceuticals.

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Comments on the Theoretical vs Practical Aspects of Threshold Limit Value

Apparently, neither OSHA (1994) nor EPA (1992) considered it meaningful that ETS is an extremely dilute system to which a nonsmoker is exposed compared to MS inhaled by a smoker or MS and SS collected in laboratory smoke-collection apparatus. Both agencies ignored the wealth of data available from inhalation studies involving the lifetime administration of whole cigarette MS to laboratory animals: No lung tumors, similar to those claimed to be associated with cigarette smoking in humans, have been observed in animals exposed by the inhalation route to MS administered for their life span (*cf.* Huber, 1989). However, in similar inhalation studies with the exhaust gases from internal combustion engines, *e.g.*, Diesel engines, lung tumors of the type observed in humans were produced in the exposed animals (Mauderly *et al.*, 1987).

OSHA also ignored the fact that progressive reduction (or successive dilution) of the dose of an administered material which produced a given effect eventually leads to a dose level at which no effect is observed. Despite numerous data available to contradict it, the theory to which many researchers agree is that the only safe threshold limit value for a material tumorigenic in humans is a "zero" dose. This concept is difficult to refute theoretically but, practically, there is obviously a threshold limit value. Many investigators extrapolate this theory to compounds such as BaP and similar PAHs for which there is either no hard evidence of tumorigenicity in man or, if the theory were correct, cancer in man would be even more extensive than it currently is because of the ubiquity of PAHs such as BaP.

The scientific literature is replete with studies demonstrating the presence of PAHs such as BaP in many foodstuffs in the average diet. In fact, in his review on PAHs in foodstuffs, Maga (1988) listed all but one (5-methylchrysene) of the PAHs in the "Lists of 43" (**Table 4**) as foodstuff components. He listed 65 common PAH-containing diet ingredients and noted that in each case where the ingredient was heated in its preparation, the PAH content increased dramatically, *e.g.*, the BaP content of a single serving of charcoal-broiled meat is more than 600 times that in the MS of a single cigarette. Maga noted that the average daily intake of BaP (charcoal-broiled meat excluded) in the diet is estimated at about 500 ng. Other non-PAH tumorigens at levels far in excess of that of BaP in cigarette MS are encountered in numerous other dietary articles. If BaP were tumorigenic in man and the "zero" threshold limit value were applicable, the incidence of cancer of the digestive tract would be substantially higher than it is.

Considerable laboratory evidence is available which demonstrates that exposure of laboratory animals to lower and lower doses of CSC or to lower and lower doses of several of its PAH components, *e.g.*, BaP, DBA — reported to be potent mouse-skin tumorigens and alleged to be carcinogenic to humans — results in successive diminution of the tumorigenicity until it ceases to be observed, *i.e.*, no tumors are generated in the CSC- or PAH-treated animals at a sufficiently diminished dose.

The progression to lower and lower doses used in such studies may validly be considered

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equivalent to the dilution in ETS which comprises diluted and aged exhaled MS plus intra- and interpuff-generated SS and whose composition is qualitatively similar to but quantitatively different from exhaled MS and intra- plus interpuff-generated SS (Rodgman, 1991, 1992).

Evidence from studies conducted in several laboratories is available to answer the following questions:

- To what extent must the skin-painting dose (in mg/day) of CSC be reduced so that no tumors are observed in the test animals? Or, expressed in another way: To what extent must a tumor-producing CSC solution, *e.g.*, 50% CSC in acetone, be diluted so that lifetime skin painting with a fixed volume of solution produces no tumors?

- Below what skin-painting application dose will CSC PAHs such as BaP or DBA fail to generate tumors in the treated animals?

- What is the difference in response of animals skin-painted with equal doses of MS CSC and SS CSC?

- What are the ETS/MS ratios (*i.e.*, the extent of dilution) for specific components and how do these ratios compare to the ratios for MS (or SS) CSC or MS components at which the tumor-generating effect totally disappears?

- How valid is the premise held by some agencies such as the OSHA and EPA and some investigators that no threshold limit value exists with respect to the tumorigenicity of the MS components listed by Hoffmann and Hecht (1990) and OSHA (1994)?

From these considerations, what would be the potential biological effects of ETS if one assumed it to be a highly diluted system of MS plus SS?

Inhalation Studies with Whole Cigarette Smoke

Wynder and Hoffmann (1964, 1967) reviewed the early studies in which attempts were made to produce squamous cell carcinoma in animals by exposing them to whole cigarette smoke via the inhalation route. Squamous cell carcinoma (bronchogenic carcinoma) is the lung tumor type usually reported to be associated with smoking in cigarette smokers, but a recent study reported the predominance of adenocarcinoma in nonsmoking females spouses of smokers (Fontham *et al.* 1991).

The smoke exposure in the early laboratory animal studies was primarily "whole body" exposure rather than inhalation exposure. Some of the smoke-treated animals did develop lung tumors of a type (adenoma) not generally associated with cigarette smoking in humans, *e.g.*, the Advisory Committee to the U.S. Surgeon General (USPHS, 1964) noted:

> The production of bronchogenic carcinomas has not been reported by anny investigator exposing

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experimental animals to tobacco smoke.

These early studies on tobacco smoke exposure were criticized because they involved "whole body" exposure of the test animal to smoke, *i.e.*, the test animals were confined in a space into which diluted fresh whole cigarette MS was directed. More recent studies (Dalbey *et al.*, 1980; LeBouffant *et al.*, 1980; Wehner *et al.*, 1981; Motulionis, 1984; Henry and Kouri, 1984, 1986; Wilbourn *et al.*, 1986) have involved smoke inhalation via the "nose-only" route. Analyses with radiolabeled *n*-dotriacontane, nicotine, and BaP revealed that the exposed animals did indeed inhale the smoke and much of the "nose-only" inhaled smoke reached the lungs (Microbiological Associates, 1984). Since the type of carcinoma reported to be associated with human smoking did not develop in the lungs of the treated animals, it was thought at one time that the adenoma was the lung tumor type characteristic of the rodent. However, similar chronic exposure of rats to Diesel exhaust gases did produce squamous cell carcinoma similar to that observed in humans (Mauderly *et al.*, 1987). As Huber (1989) noted:

> Overall, however, these bioassays for tobacco smoke have been inadequate, or perhaps ineffectively and inappropriately utilized; they have not provided acceptable analogues or models of lung cancer observed in humans...when, in fact, inhalation studies with some of the same kinds of animal bioassays and with environmental toxins not related to tobacco smoke do result in lung cancer similar to that which occurs in man.

Certain animal species develop human-type lung tumors when challenged with a variety of environmental toxins. The same species do not develop human-type lung tumors from tobacco smoke inhalation. Thus, the positive carcinoma induction with inhaled Diesel exhaust gases *vs* negative carcinoma induction with inhaled cigarette MS indicates that the latter was not primarily due to the choice of test species, the rodent. Results obtained from the early inhalation studies (Campbell, 1936; Lorenz *et al.*, 1943; Essenberg, 1952, 1954a, 1954b, 1957; Essenberg *et al.*, 1955, 1956; Leuchtenberger *et al.*, 1958, 1960a, 1960b, 1962) included the following: No effect was observed with cigarette smoke exposure but adenoma was produced by similar exposure to engine exhausts or road tars and dusts (Campbell, 1936, 1937, 1939). Adenoma but not human-type squamous cell carcinoma was produced in some mouse strains exposed to cigarette smoke. The latent period for adenoma development was reduced and the adenoma incidence was increased in the A strain mouse, 90% of which will spontaneously develop an adenoma without exposure to any tumorigenic inhalant (Shimkin, 1955).

The failure to produce in laboratory animals exposed to whole cigarette MS the tumor type reported to be associated with smoking in humans is important not only with regard to the biological properties of MS itself but also with respect to the diluted MS delivered to the caged animals. These early experiments involving "whole body" exposure of the host to diluted MS closely resemble exposure to ETS. In fact, one of the criticisms of the "whole body"-exposure technique was that it more closely simulated exposure of the nonsmokers to highly concentrated ETS than it simulated exposure of smoker to MS by inhalation, *e.g.*, Stewart and Herrold (1962) commented on the pre-1961 inhalation studies as follows:

> Another objection to the mouse-smoking experiments has been that none of them duplicates the

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habit of cigarette smoking as practiced by men and women. Mice maintained in an airtight cage into which tobacco smoke mixed with air is blown are said to be living in an environment comparable to that in which nonsmokers are collected together with heavy smokers for long hours at a time.

If, as Stewart and Herrold (1962) noted, the numerous cigarette smoke-inhalation experiments prior to 1962 more closely resembled exposure to passive smoke (or ETS) than they mimicked human exposure during active smoking, then there is a wealth of laboratory evidence available which demonstrates that exposure to "passive smoke" (or ETS), more concentrated than usually encountered in the human environment, is ineffective in induction of the tumor type supposedly associated with cigarette smoking in humans: All of the "whole body"-exposure studies (*e.g.*, Campbell, 1936; Lorenz *et al.*, 1943; Essenberg, 1952, 1954a, 1954b, 1957; Essenberg *et al.*, 1955, 1956; Leuchtenberger and Leuchtenberger, 1962; Leuchtenberger *et al.*, 1958, 1960a, 1960b) were originally designed to determine the biological effect of MS on laboratory animals, with particular emphasis on lung cancer induction. However, because of the way the experiments were conducted (essentially "whole body" exposure), their results are relevant to the evaluation of the biological effects of exposure to a concentrated "passive smoke" (or ETS). None of these exposures to concentrated "passive smoke" (or ETS) induced human-type carcinoma in the test animals.

In its report, OSHA (1994) appears to be trying to confuse the reader by its selection of inhalation studies for comment. After stating the following:

> Currently, OSHA is aware of only a few experimental inhalation studies with sidestream smoke or ETS reported in the literature. A discussion of these studies follows.

and implying that the studies to be discussed will deal with data generated for either ETS or SS, OSHA (1994: page 15980) then proceeds to chronicle the biological responses observed in 14 different studies conducted with laboratory animals: 11 of the studies deal with MS exposure via inhalation, one deals with SS exposure via implantation not inhalation (Grimmer *et al.*, 1988), and only two of the studies actually deal with ETS exposure via inhalation (Coggins *et al.*, 1992, 1993).

The 11 inhalation studies selected for discussion by OSHA included the following:

- Holland *et al.* (1963): No tumors were seen in rabbits exposed to MS for up to 5.5 years.
- Auerbach *et al.* (1970): Lung tumors observed in beagle dogs exposed to MS from nonfiltered cigarettes.
- Bernfeld *et al.* (1974): Hyperplasia observed in the larynxes of hamsters exposed to MS.
- Dontenwill *et al.* (1974): Laryngeal leukoplakia observed in MS-exposed hamsters.
- Harris *et al.* (1974): Four lung tumors and emphysema were detected in male and female C57Bl mice, exposed "nose-only," to fresh MS.
- Davis *et al.* (1975): Pulmonary squamous neoplasms were detected in female Wistar rats exposed to 1:5

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